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MICROWAVE-ASSISTED SYNTHESIS OF PHENOTHIAZINE SULFOXIDE DERIVATIVES

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ABSTRACT: Microwave assisted oxidation of 10-alkyl-phenothiazine derivatives with copper(II) nitrate selectively generated phenothiazine-sulfoxides in very short reaction times (1-2 minutes). Best results were obtained by dry media procedure using silica gel solid support, a fact which opens a path for environmentally safe procedures envisaged by green chemistry. The structure of the products was assigned by IR and high resolution NMR spectroscopy.

Keywords: *10-alkyl-phenothiazine-sulfoxides*, *copper(II) nitrate oxidizing agent*, *Microwave assisted organic synthesis (MAOS)*

INTRODUCTION

Various oxidation products of phenothiazine were obtained when a wide range of chemical oxidants were employed (hydrogen peroxide, potassium permanganate, nitric acid, potassium hypochlorite, chromic anhydride, sodium nitrite, etc. [1]. As shown in scheme 1, the phenazathionium cation formed by the loss of 2 electrons and a proton from the parent heterocycle may be considered as a key intermediate in the formation of oxidized products. Formal hydration of the cation quinoid structure by addition of water may proceed at C-3, at S or at N, thus yielding 3H-phenothiazin-3-one **1**, phenothiazine 5-oxide **2** and phenothiazine nitroxyl **3** respectively [2].

Hydrogen peroxide was extensively used as an effective reagent for the synthesis of phenothiazine-5-oxide **2** derivatives, but the excess amounts of this reagent produces phenothiazine 5,5-dioxide derivatives [3-5].

Phenothiazine 5-oxide **2**, was obtained selectively and in good yields in the presence of alkyl-hydroperoxides [6], but poor yields were observed when electron withdrawing substituents were attached to the heterocyclic substrate. N-alkyl- phenothiazine-5-oxide derivatives were also successfully prepared using *m*-chloroperbenzoic acid [7].

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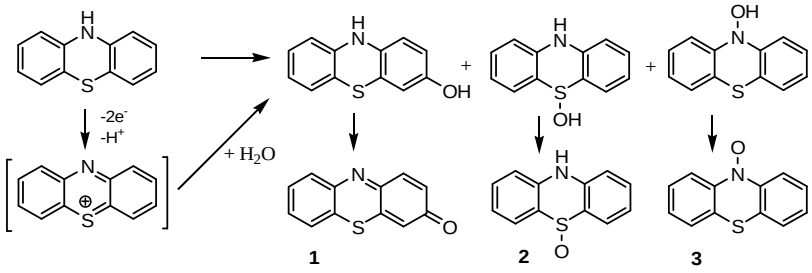


Scheme 1.

Nitric acid can be used as an oxidizing agent for phenothiazine sulfoxide preparation [7,8], but competitive substitution may occur in position 3 of the phenothiazine substrate. Catalytic autooxidation of N-alkyl-phenothiazine derivatives in the presence of nitroxides (NO_2, $NOBF_4$) or HNO_2 selectively generates phenothiazine-5-oxide derivatives [9]. Compounds containing pyrazolines, enones and oxo functional groups attached to phenothiazine core unit, were selectively transformed into sulfoxides by the effect of ultrasound-promoted oxidation with copper(II) nitrate [10]; this method generated high yields of sulfoxides (sometimes reaching 95%), irrespective of the ring substituents, in relatively short reaction times.

The aim of this work was to test the efficiency of microwave assisted organic synthesis (*MAOS*) techniques in the preparation of phenothiazine sulfoxides by the oxidation of phenothiazine substrates with copper(II) nitrate and to compare this technique with the previously reported ultrasound-promoted oxidation, having in view that *MAOS* technique may afford certain advantages such as shorter reaction times and sometimes higher reaction selectivity [11,12]. An increasing need for less hazardous reaction conditions and environmentally safe procedures, or green chemistry, guided the chemical synthesis towards solvent free reactions approach, highly reproducible under *MAOS* techniques.

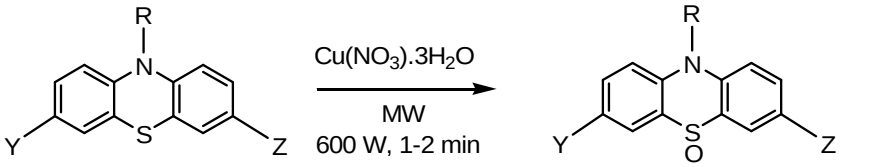
RESULTS AND DISCUSSIONS

In order to ensure a high reproducibility of our experiments the technique applied is based on microwave power processing of materials using a microwave installation *Synthos 3000* equipped with temperature and pressure sensors, built-in magnetic stirrer, cooling mechanisms, power control and software operation.

According to the sample preparation, several methods have been developed for operating microwave-assisted syntheses: reactions in the presence of solvent (in solution phase or polymer-supported solid phase),

or solvent-free syntheses (which fall into three categories: reactions with neat reactants, reactions under phase transfer catalysis and reaction mixtures adsorbed onto inorganic supports). Microwave-assisted selective oxidation of sulfides to sulfoxides and sulfones was studied by Varma and co-workers, who employed different oxidants on supported mediums in solvent free reaction environments (such as wet silica-supported sodium periodate [13], or copper(II)nitrate on clay-hidrogen peroxide [14]).

Oxidation with copper(II) nitrate was applied to several 10-alkyl-phenothiazines and found that S-oxidation took place selectively resulting in sulfoxides irrespective of the ring substituents (scheme 2). On the effect of the "*in situ*" generated nitrogen-dioxide [15] oxidation of heterocyclic sulfur atom occurred, leading to sulfoxides in good to high yields. The reaction can be induced by conductive heating, ultrasounds promoted or microwave assisted.



4 R= -Me, Y= Z = -H
5 R= -Me, Y= H Z= -CHO
6 R= -Me, Y= Z= -CO-CH_3

Scheme 2

Under thermal procedure, 10-methyl phenothiazine afforded 78% yield of 10-methyl-phenothiazine-5-oxide after 3 hours at 40 ^{o}C, but sonication accelerated the oxidation in such a way that 90% yields were obtained after 45 minutes of sonication at room temperature [10]. A direct comparison between the microwave assisted and the ultrasound promoted oxidation reaction can be considered by using the same reaction mixture and changing the source of energy. Two microwave-assisted methods were selected for the sample preparation: i) synthesis in the presence of solvent and ii) solvent free synthesis using reaction mixture adsorbed onto inorganic supports. Table 1 summarizes the results obtained in the microwave assisted oxidation of 10-alkylphenothiazine derivatives with copper(II) nitrate, in comparison with sonication data.

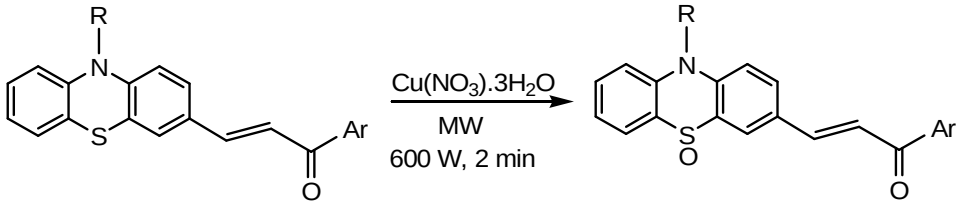
Dichloromethane solvent employed in the sonication experiments is a low microwave absorbing solvent (dielectric loss value 0.382 [16]) and moderate reaction yields were obtained when this solvent was employed in the microwave assisted oxidation (Table 1).

Table 1. Microwave assisted *versus* sonication data obtained for the oxidation of 10-alkylphenothiazine derivatives with copper(II) nitrate.

Cpd.	MAOS					Sonication [10]	
	Power [W]	DCM solution		SiO_2 solid support			
		T [min]	Yield [%]	T [min]	Yield [%]	T[min]	Yield [%]
4	600	2	65	1	90	60	95
5	600	2	35	1	60	60	90
6	600	2	43	4	60	60	85
7	600	2	33			60	86
8	600	2	23			60	70
9	600	2	42			60	80

The oxidation of phenothiazine derivatives was also performed in dry media conditions using adsorbed reagents on solid support, a procedure which reduces the amount of solvent used and minimize potentially hazardous reactions (dichloromethane and chloroform can generate highly toxic products HCl, CO, CO_2 and phosgene, due to prolonged exposure to high temperatures). Two different support materials were tested: alumina (which can act as a base) and silica gel (which can act as an acid). *MAOS* on solid support required only 1 minute of irradiation to yield 90% phenothiazine-sulfoxide on silicagel. On the contrary, phenothiazine-5-oxide derivatives were not obtained when Al_2O_3 was employed as solid support.

In compound **6** the formyl group was not affected by oxidation in the *MAOS* conditions employed. Satisfactory results were obtained for the oxidation of 10-methyl-3,7-diacetyl-phenothiazine, which may be considered as a substrate resistant to oxidation. 10-Alkyl-phenothiazinyl-enones were subjected to the same oxidizing conditions (scheme 3) and S-oxidation occurred in lower yields in the case of *MAOS* as compared to sonication.



7 R= -Me, Ar= *m*-NO_2-C_6H_4
8 R= -Me, Ar= *p*-OMe-C_6H_4
9 R= -Me, Ar= 2-$C_{10}H_7$

Scheme 3

Structural assignments of sulfoxides **4-10** were based on FTIR and ^{1}H-NMR spectra. In the IR spectrum of **4-10** a very intense absorption band due to SO stretching vibration (ν_{SO}) appears situated at 1020-1025 cm^{-1}. The electron withdrawing SO group induced an important deshielding upon neighboring atoms, mainly proton and carbon atoms in positions 4,6 of the heterocyclic structure (for example in the structure of compound **4,** $\delta_{H4,6}$=8.58 ppm).

10*H*-phenothiazin-5-oxide could not be obtained by microwave assisted oxidation of 10*H*-phenothiazine with $Cu(NO_3)_2$, neither in DCM solution, nor in solvent free conditions.

CONCLUSIONS

The oxidation with copper(II) nitrate represents an advantageous method of preparation for 10-alkyl-phenothiazine-sulfoxides, due to its chemo-selectivity and potential to produce sulfoxides in high yields. Comparable results were obtained when sonication and microwave assisted synthesis were applied. Advantages of *MAOS* lie on very short reaction times (1-2 minutes). Best results were obtained by *MAOS* on silica gel solid support, a fact which opens a path for environmentally safe procedures envisaged by green chemistry.

EXPERIMENTAL SECTION

Microwave installation *Synthos 3000 Anton Paar*
300 MHz *Brucker* NMR spectrometer
Brucker Vector 22 FT-IR spectrometer
Reagents from *Merck* were used.
TLC was used to monitor the reaction progress (Merck silica gel F 254 plates).

General procedure for microwave assisted oxidation

i) in dichloromethane solution
The 10-alkyl-phenothiazine derivative (1 mmol**)** and $Cu(NO_3)_2x3H_2O$ (0.726 g, 3 mmol) were dissolved in DCM (20 cm^3). The reaction mixture was irradiated for 1-2 min (table 1) using power settings 600W. The reaction was monitored by TLC. After completion, the reaction medium was filtered and the solid was washed with DCM (2 x 20 cm^3). After evaporation the residue obtained was purified by column chromatography on silica using DCM-MeOH (15-1) as eluent and re-crystallised from EtOH.

ii) on silica gel solid support
The 10-alkyl-phenothiazine derivative (1 mmol**)** was dissolved in DCM (20 cm^3), 1g silica gel was added and the solvent was evaporated to dryness under vacuum. The solid product was mixed with $Cu(NO_3)_2x3H_2O$ (3 mmol). The

reaction mixture was irradiated for 1-2 min (table 1) using power setting 600W. The reaction product was extracted in DCM. After evaporation the residue obtained was purified by column chromatography on silica gel using DCM-MeOH (15-1) as eluent and re-crystallised from EtOH.

10-Methyl-10*H*-phenothiazine-5-oxide 4
White powder; mp 187-189 ℃ (lit.: 193 ℃ [17])
IR (cm^{1}): 2085, 1584, 1457, 1261, 1020, 765
^{1}H-RMN, $CDCl_3$: δ(ppm) =3.79 (s, 3H); 7.27 (*t*, 2H); 7.40 (*d*, 2H); 7.64 (*t*, 2H); 7.95 (*d*, 2H).

3-Formyl-10-methyl-10*H*-phenothiazine-5-oxide 5
Yellow powder; (0.232 g, 90%); mp 205-207 ℃; (lit. : 207-208 ℃)
IR (cm^{1}): 2090, 1682, 1605, 1462, 1260, 1046, 1025, 764, 751
^{1}H-RMN, $CDCl_3$: δ(ppm) =3.80 (*s*, 3H); 7.34 (*t*, 1H); 7.46 (*m*, 2H); 7.65 (*t*, 1H); 7.94 (*d*, 1H); 8.08 (*d*, 1H); 8.39 (s, 1H); 9.97 (s, 1H).

3,7-Diacetyl-10-ethyl-10*H*-phenothiazine-5-oxide 6
Yellow powder; (0.278 g, 85%); mp 259-262 ℃;
IR (cm^{1}): 2085, 1674, 1589, 1479, 1249, 1024, 826.
^{1}H-RMN, $CDCl_3$: δ(ppm) =2.68 (s, 6H); 4.45 (s, 3H); 7.58 (*d*, 2H); 8.29 (*d*, 2H); 8.58 (*s*, 2H).

(*E*)-10-Methyl-3-[1-(3-nitrophenyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide 7
Yellow powder; (0.348 g, 86%); 201 -204 ℃
IR (cm^{1}): 1656, 1586, 1466, 1218, 1021, 813, 754.
^{1}H-RMN, $CDCl_3$: δ(ppm) =3.80 (s, 3H); 7.29 (m, 3H), 7.54 (d, 1H), 7.64 (m, 1H), 7.7 (t, 1H), 7.9 (m, 3H), 8.22 (s, 1H), 8.6 (d, 2H), 8.81 (s, 1H).

(*E*)-10-Methyl-3-[1-(4-methoxyphenyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide 8
Yellow powder; (0.272 g, 70%); 237 -241 ℃;
IR (cm^{1}): 1654, 1602, 1585, 1463, 1259, 102o, 834, 805.
^{1}H-RMN, $CDCl_3$: δ(ppm) =3.78 (s, 3H); 3.90 (s, 3H); 6.99 (d, 2H); 7.31 (d, 1H); 7.4 (m, 2H); 7.56 (d, 1H); 7.65 (t, 1H), 7.83(m, 2H), 7.96 (d, 1H); 8.06 (d, 2H), 8.21 (s, 1H).

(*E*)-10-Methyl-3[1-(2-naphthyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide 9
White powder; (0.327 g, 80%); 225-226 ℃
IR (cm^{1}): 1654, 1586, 1465, 1261, 1020, 810, 747
^{1}H-RMN, $CDCl_3$: δ(ppm) =3.78 (s, 3H); 7.33 (t, 1H); 7.41 (m, 2H); 7.66 (t, 1H); 7.73 (d, 1H); 7.9 (d, 2H), 7.96 (m, 6H), 8.13 (d, 1H); 8.30 (s, 1H), 8.60 (s, 1H).

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